

# Standard variables fail to identify patients who will not respond to fluid resuscitation following thermal injury: brief report☆☆☆

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## Abstract

Approximately 13% of thermally injured patients fail resuscitation, in that they die during the first 48 h postburn despite full resuscitative efforts. The purpose of this study was to characterize these patients, and to develop a predictor of resuscitation failure.

**Methods:** Records of 3807 thermally injured patients admitted to this burn centre during 1980–1997 were reviewed. Patients were classified as surviving to hospital discharge (“NONFAIL/LIVE”), as surviving resuscitation but dying later (“NONFAIL/DIE”), or as failing resuscitation (“FAIL”). Ordinal logistic regression was used to develop a predictor of membership in each of these three groups.

**Results:** With respect to total burn size, full thickness burn size, and inhalation injury, the three groups represented a gradation in injury severity from least severe (NONFAIL/LIVE) to most severe (FAIL). The predictive model had an overall accuracy of 91.6%; however, it correctly classified NONFAIL/LIVE patients more often (97.7% accuracy) than it did NONFAIL/DIE patients (57.5%) or FAIL patients (16.1%).

**Conclusion:** Patients who failed resuscitation were more severely injured than those who survived resuscitation, but was not possible accurately to predict who will fail resuscitation using data available on admission.

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## 1. Introduction

The definition of the fluid resuscitation requirements of burn patients as a function of the total body surface area burned (TBSA) and the preburn weight [1,2] led to the virtual elimination of acute renal failure as a consequence of burn shock [3] and reduced the early postburn death rate. Nevertheless, failure of resuscitation, defined as death within 48 h of hospitalization despite full efforts to resuscitate, has constituted approximately 13% of deaths in recent years at this institution [4]. Clearly, new

resuscitative strategies would be needed to salvage these patients; alternatively, it is also conceivable that some of these patients might not be salvageable even with new therapies. In either case, no data exist which allow the early identification of such patients. The purpose of this study was to review our experience with failure of resuscitation and to evaluate our ability to predict this outcome, based on data commonly available upon admission.

## 2. Methods

This retrospective study was approved by the Institutional Review Board. The records of the 4115 thermally injured patients admitted to the U.S. Army Burn Center during a 17-year period, 1980–1997, were reviewed. This period was chosen because an aggressive therapeutic approach led to efforts at resuscitation in all but a handful of cases.

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☆☆ The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Moreover, a consistent approach to fluid resuscitation was employed throughout. The modified Brooke formula was used to estimate fluid resuscitation requirements during the first 24 h as lactated Ringer's solution (LR), 2 ml/kg/% burn [5], or as 3 ml/kg/% burn for children weighing less than 30 kg [6]. The LR infusion rate was adjusted based on physiologic response; a urine output of 30–50 ml/h for adults, or 1 ml/kg/h for children, was the primary indicator of adequacy of resuscitation [7]. Burn size was determined by means of the Lund-Browder chart. Inhalation injury was diagnosed by fiberoptic bronchoscopy or xenon-133 lung scanning [8,9]. No attempt was made to score inhalation injury severity, since no widely accepted index of inhalation injury severity exists [10]. Inclusion criteria for the study were admission or transfer within 48 h of injury to this burn centre, burns of any size, and patients of any age. Exclusion criteria were electric, chemical, or severe mechanical trauma (the transfusion of blood per se was not exclusionary).

The patient classification scheme used in this study is shown in Fig. 1. Patients who died within 48 h of injury despite resuscitative efforts were classified as patients with failure of resuscitation (FAIL). Patients for whom there was a documented decision to withhold, to decrease, or not to escalate care during the 48 h postburn period were classified as “early do-not-resuscitate patients” (DNR/EARLY), and were excluded from the study. Patients who survived the 48 h resuscitation period, but later died, were termed NONFAIL/DIE patients. Patients who survived the hospital stay were termed NONFAIL/LIVE patients. (No effort was made to identify NONFAIL/DIE patients who died with a DNR order in place.) The 48 h cut point was chosen in order to be consistent with previous reports on failure of resuscitation [4], and because plasma volume is restored in most patients by that time point [11]; thus, our practice is

to change fluid therapy at that time point from therapy directed at restoration of plasma volume, to therapy directed at replacement of evaporative water losses and gradual diuresis of the resuscitation load [7]. Data collected included age of patient, sex, total burn size (TBSA), full thickness burn size (FULL), presence of inhalation injury (INHAL), and year of injury.

Statistical analysis employed SPSS v. 10.1 (Chicago, IL). Univariate analysis employed the chi-square test for categorical variables. Continuous variables (TBSA, FULL, YEAR, Age) were evaluated with the Kolmogorov–Smirnov and Shapiro–Wilk tests, and were found not to be normally distributed. Therefore, groups were compared by Kruskal–Wallis tests and post hoc Mann–Whitney *U*-tests, with Bonferroni correction of *p*-values for three non-orthogonal comparisons.

NONFAIL/LIVE, NONFAIL/DIE, and FAIL groups were compared, while DNR/EARLY patients were excluded from subsequent analysis. Based on the results of univariate analysis (see below, Table 1), it appeared that there was a progression in severity of injury, with the NONFAIL/LIVE group having injuries of lowest severity, the NONFAIL/DIE group having injuries of intermediate severity, and the FAIL group having injuries of highest severity. This progression held true for TBSA, FULL, and INHAL.

This allowed us to generate a new ordinal variable, Mortality Group, with values of 1, 2, or 3: where 1 means survival, 2 means death after the first 48 h postburn, and 3 indicates death within the first 48 h postburn. Ordinal logistic regression (Polytomous Universal Model, or PLUM procedure) is a multivariate statistical procedure used to analyze ordinal variables such as this. It was used to identify independent variables predictive of membership in each of the three groups. In addition, exact binomial expansion was

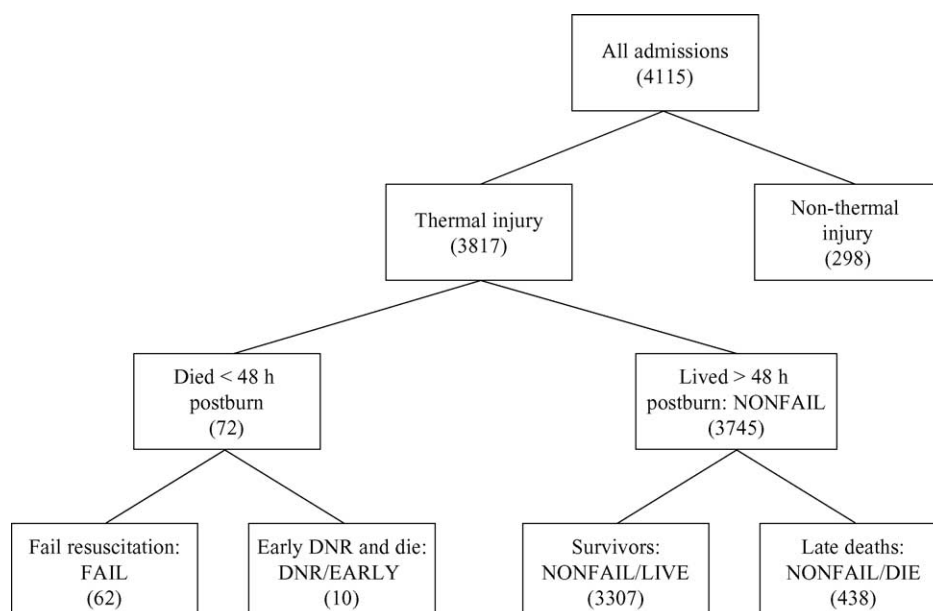


Fig. 1. Categorization scheme for the study.

Table 1  
Basic data for patients in the study

Group	<i>n</i>	Age <sup>a,b</sup>	Sex <sup>d</sup>	TBSA <sup>a,b,c</sup>	FULL <sup>a,b,c</sup>	INHAL <sup>d</sup>	YEAR <sup>a,b</sup>
1	3307	27.5 ± 19.2	79.7	18.3 ± 16.7	6.7 ± 12.3	19.3	89.5 ± 5.2
2	438	46.3 ± 23.7	74.0	55.0 ± 24.0	38.2 ± 26.3	65.8	86.3 ± 5.3
3	62	39.2 ± 26.4	83.9	70.7 ± 24.3	60.1 ± 31.7	80.6	86.1 ± 5.3
4*	10	72.7 ± 14.5	80.0	56.8 ± 31.1	40.9 ± 33.3	90.0	95.8 ± 1.1

Group 1, NONFAIL/LIVE; group 2, NONFAIL/DIE; group 3, FAIL; group 4, DNR/EARLY. Age, age in years; sex, percentage of males in this category; TBSA, total body surface area burned, percent; FULL, full thickness burn size, percent; INHAL, percentage of patients in this category with inhalation injury; YEAR, year of injury.

<sup>a</sup> Significant difference between groups 1 and 2.

<sup>b</sup> Significant difference between groups 1 and 3.

<sup>c</sup> Significant difference between groups 2 and 3.

<sup>d</sup> Significant difference among the groups for the 3 × 2 chi square test.

The *p* value for all tests was < 0.001, except as follows: Age, groups 2 vs. 3:

*p* = 0.084. Year, groups 2 vs. 3: *p* = 0.909. Sex, 3 × 2 chi square test: *p* = 0.014.

\* The DNR/EARLY patients were excluded from analysis.

used to compare observed mortality in the FAIL group, to mortality predicted by a logistic regression (backward likelihood-ratio) equation generated from data for all 3818 thermally injured patients admitted during the study period [12].

The relationship between age and burn mortality can be modeled by a cubic equation which incorporates age, age squared, and age cubed [13]. This models the observation that starting at birth, mortality decreases as age increases and reaches a nadir at about age 21; thereafter it increases with increasing age; then in old age it levels off. For this reason, age was represented in these multivariate analyses by the following function, which was derived empirically from a large series of patients at this center:

$$\text{age function} = -5 \times \text{age} + 14 \times \frac{\text{age}^2}{100} - 7 \times \frac{\text{age}^3}{10000}$$

Significance was accepted at *p* < .05. Data are presented as means ± S.D.

### 3. Results

Of the 3817 patients admitted to the burn centre with a primary diagnosis of thermal injury during the study period and excluding those with life-threatening mechanical trauma a total of 510 (13.4%) did not survive to hospital discharge (Fig. 1). Sixty-two patients (12.2% of the deaths, or 1.6% of all thermally injured patients) were classified as FAIL patients, who died within 48 h of injury despite full resuscitative efforts. Another 10 (2.0% of the deaths, or 0.3% of all thermally injured patients) were classified as DNR/EARLY patients, who died during the first 48 h with a DNR order in place. Thus, a total of 72 patients (14.1% of the deaths, or 1.9% of all thermally injured patients) died within 48 h of injury. Results of univariate analysis are shown in Table 1; the data are also depicted graphically in Figs. 2–5.

Based on univariate analysis of the TBSA, full-thickness burn size, and inhalation injury variables (Table 1), it was evident that injury severity progressively increased from the

NONFAIL/LIVE group, through the NONFAIL/DIE group, to the FAIL group. We therefore sought to discriminate predictors of membership in each of these three groups by means of ordinal logistic regression. The DNR/EARLY patients were excluded from this analysis, leaving 3807 in the three groups. The following independent variables were submitted to this procedure: AGEFN (the cubic age function), FULL (full-thickness burn size), TBSA, YEAR (year of admission), and INHAL (inhalation injury, 1 if present, 0 if absent). The dependent variable, which we termed mortality group, has 3 possible values: 1 for NONFAIL/LIVE, 2 for NONFAIL/DIE, and 3 for FAIL. The results of the analysis are given by the following equations:

$$P(Y = 1) = \frac{e^x}{1 + e^x}$$

where

$$x = -1.4210 - 2.1882 \times \text{AGEFN} - 0.0261 \times \text{FULL} - 0.0586 \times \text{TBSA} - 0.0724 \times \text{YEAR} - 0.8277 \times \text{INHAL}.$$

$$P(Y = 2) = \frac{e^x}{1 + e^x} - P(Y = 1)$$

where

$$x = 2.5350 - 2.1882 \times \text{AGEFN} - 0.0261 \times \text{FULL} - 0.0586 \times \text{TBSA} - 0.0724 \times \text{YEAR} - 0.8277 \times \text{INHAL}.$$

$$P(Y = 3) = 1 - [P(Y = 1) + P(Y = 2)]$$

By solving each of the above equations for a given patient, the probability of membership in each of the three groups can be calculated. This was done for all 3807 patients, and predicted versus actual group membership was compared. A correct prediction for a given patient was defined as correspondence between predicted and actual group membership. Based on this approach, the overall accuracy of the model is 91.6%; that is, it correctly predicted group membership in 3486 of the 3807 cases. We also determined, for each of the three groups, the ability of the model to predict membership in that particular group. The results of this subgroup analysis are presented in Fig. 6 and Table 2. Accuracy for the NONFAIL/LIVE group was 97.7%; for the NONFAIL/DIE group it was 57.5%; and for

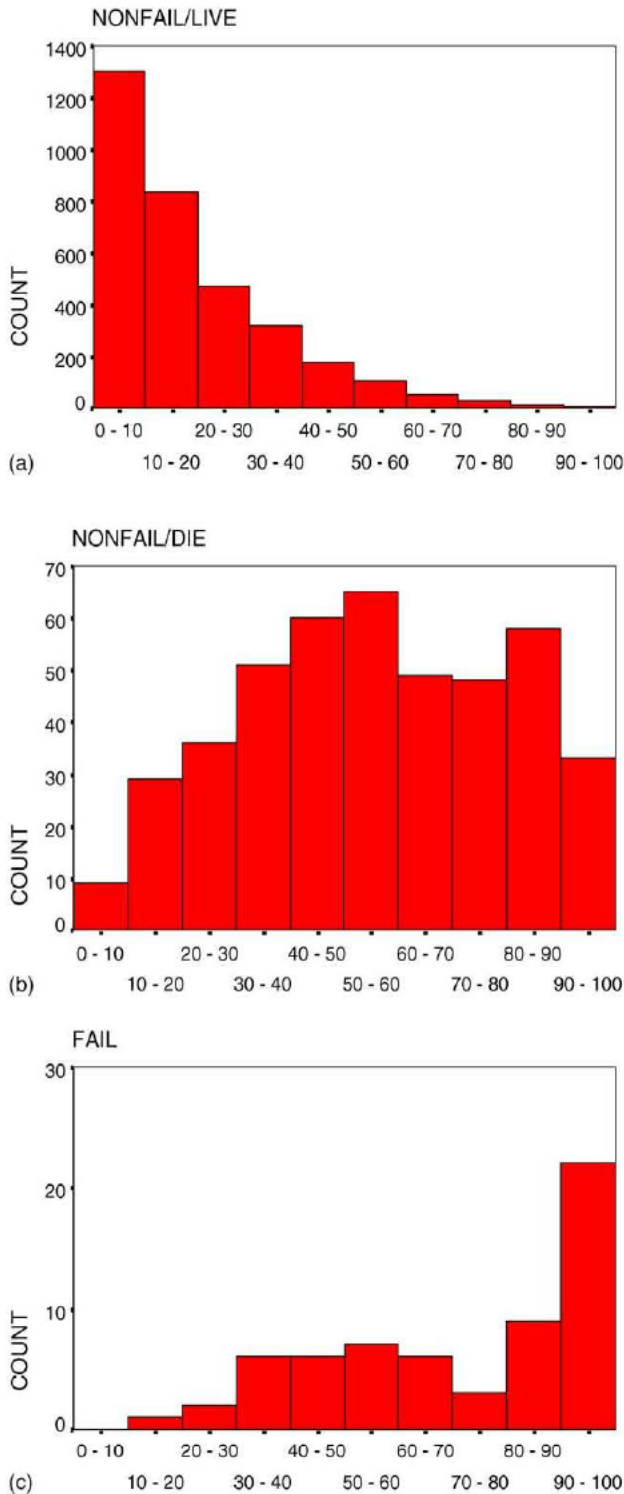


Fig. 2. Cancio et al., resuscitation failure. (a) (c) Total body surface area burned.

the FAIL group it was 16.1%. It can be seen that the model performs well for survivors (NONFAIL/LIVE), but progressively poorly for the other groups.

Information about the 10 DNR/EARLY patients is summarized in Table 3. As can be seen, many of these patients were terminally ill upon injury.

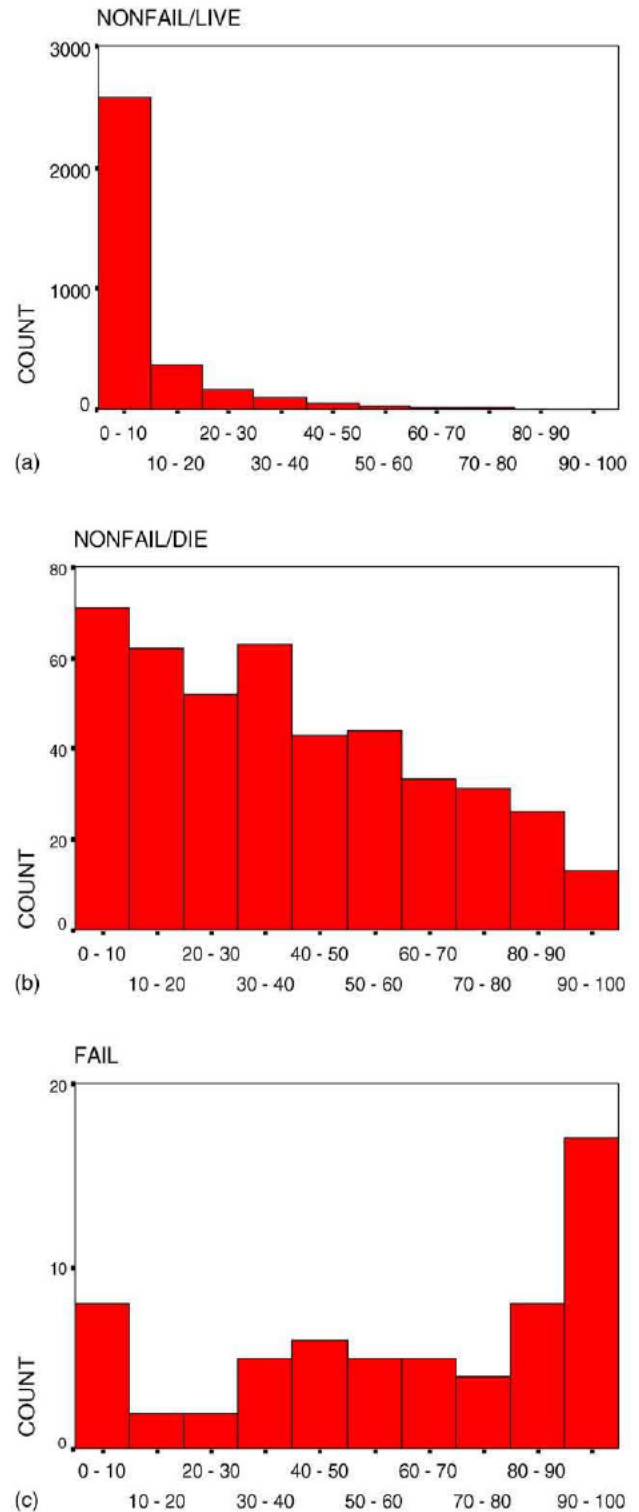


Fig. 3. Cancio et al., resuscitation failure. (a) (c) Full thickness burn size.

#### 4. Discussion

The principal finding in this study is that it is not possible accurately to predict who will fail resuscitation based on a patient's age, burn size, and presence of inhalation injury. Although the overall accuracy of the ordinal logistic

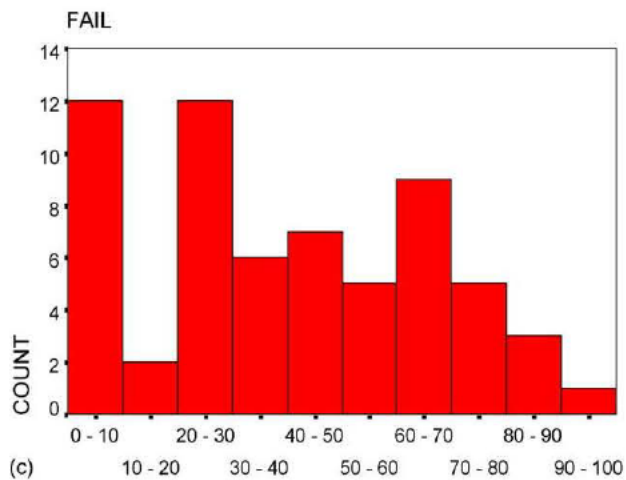
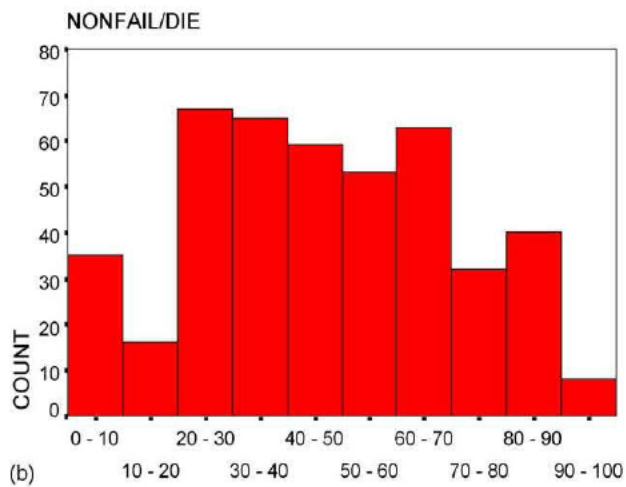
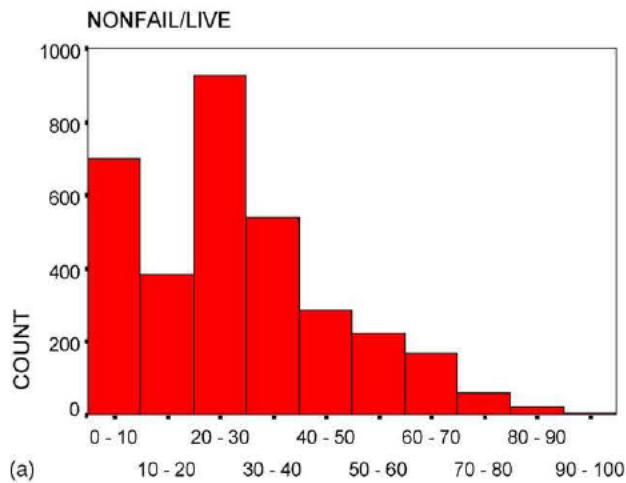


Fig. 4. Cancio et al., resuscitation failure. (a) (c) Age (years).

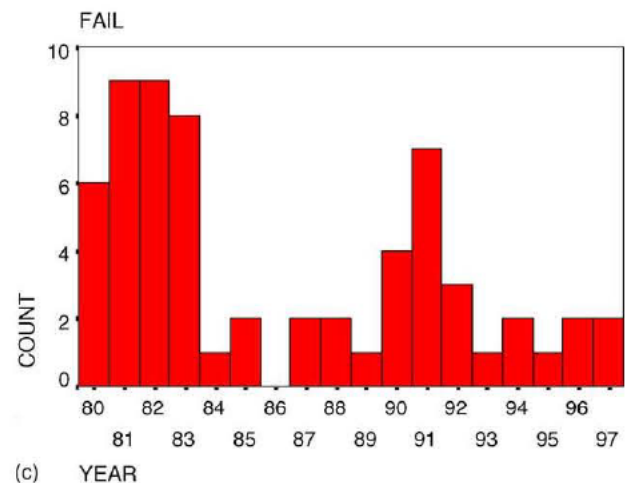
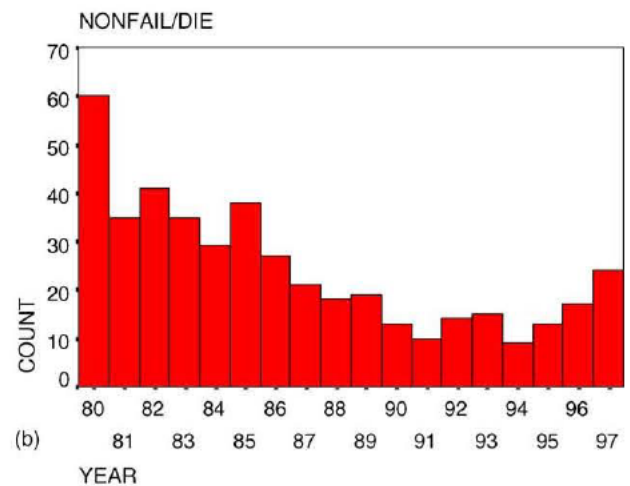
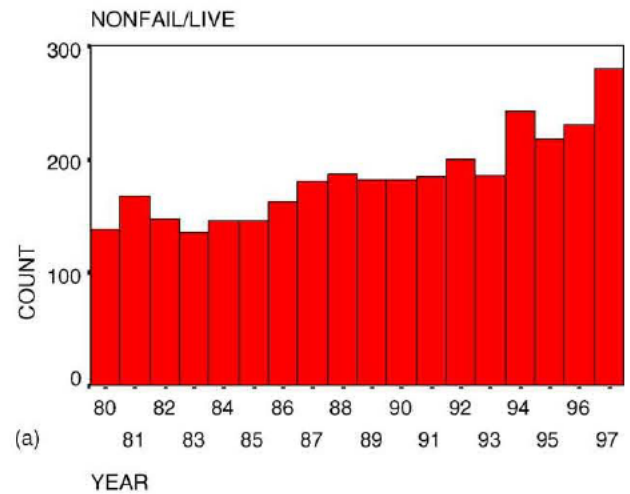


Fig. 5. Cancio et al., resuscitation failure. (a) (c) Year of injury.

regression model was 91.6%, it correctly classified the FAIL patients with an accuracy of only 16.1%. The model (see Table 2) would have incorrectly predicted failure of resuscitation for 17 of the NONFAIL/DIE patients, and, perhaps of even greater concern, would have incorrectly

predicted death for 77 of those patients who went on to survive through hospital discharge.

These findings are consistent with those recently reported by Spies et al. for pediatric burn patients. In that study, a binomial logistic regression model incorporating age, burn



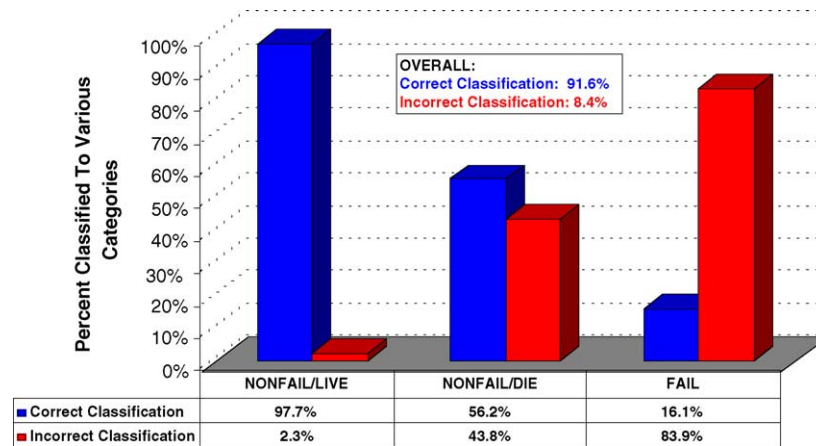


Fig. 6. Cancio et al., resuscitation failure. Accuracy of the ordinal logistic regression model.

Table 2

Ordinal logistic regression model: comparison of actual vs. predicted classifications

		Group classified to		
		1	2	3
Group classified from	1	3230	77	0
	2	175	246	17
	3	12	40	10

Group 1, NONFAIL/LIVE; Group 2, NONFAIL/DIE; Group 3, FAIL. NONFAIL/LIVE patients were preferentially classified as such by the model, with only 77 of these patients classified into the NONFAIL/DIE group, and none into the FAIL group. NONFAIL/DIE patients were preferentially classified as such by the model; inaccurate classification into the NONFAIL/LIVE group was more common than into the FAIL group. Finally, FAIL patients were classified by the model into the NONFAIL/DIE group more often than into the other two groups.

size, and inhalation injury correctly predicted mortality in only 51% of cases. Addition of pre-hospital transport and admission data had a marginal effect on accuracy. Addition of hospital course data (renal failure, need for inotropic support, sepsis, thrombocytopenia, and ventilator dependence) greatly improved accuracy [14]. This finding, and the results of the present paper, both argue in favor of an

aggressive approach to the resuscitation of most burn patients. In addition, increasing evidence points to genetic polymorphism as a factor influencing outcome in a variety of disease states, to include sepsis and trauma [15–19]. It is possible that a better understanding of the relationship between genetic factors and postburn outcome may eventually allow us to predict outcome more accurately on admission; more importantly, it may also allow us to individualize therapy based on expected pathophysiology.

No attempt was made in this study to understand, in detail, the cause of early death-only to predict it. The term “failure of resuscitation,” used in this study, indicates death during the resuscitation period despite application of our usual procedures for fluid resuscitation. More work is needed in order to uncover the reasons why some patients do not respond to resuscitation in the usual fashion.

Subject to these caveats, the following additional observations can be made. First, burn size and inhalation injury which are well known to be associated with increased mortality following thermal injury [20] were found also to be associated with earlier death, i.e. failure of resuscitation. Second, some improvement in resuscitation success was seen, by the retention of year of injury as an

Table 3

Characteristics of patients dying within 48 h of injury with a Do Not Resuscitate order (DNR/EARLY)

Age	TBSA	FULL	INHAL	Past History	Current History
80.9	37.0	25.5	1	COPD, diabetes	Acute renal failure
75.0	83.0	71.0	1	CHF, diabetes	Acute MI
78.9	9.0	1.0	1	COPD, CVA, diabetes	Arrest at scene
93.0	9.0	.0	1	COPD (O2 dependent)	Arrest at scene
66.1	59.5	15.0	1	Mental retardation	Acute MI
81.4	66.5	21.0	1	CVA, living will, ETOH abuse	
65.1	94.0	89.5	1	MIIs, CVA, organic brain disease	
48.5	85.0	64.0	0	Prior suicide attempts	Suicide
52.3	81.0	81.0	1	Living will	
86.2	44.0	41.0	1	Metastatic prostate cancer	

Age, age in years. TBSA, total body surface area burned, percent. FULL, full thickness burn size, percent. INHAL, presence (1) or absence (0) of inhalation injury. YEAR, year of injury. COPD, chronic obstructive pulmonary disease. CHF, congestive heart failure. CVA, history of cerebrovascular accident. ETOH, ethanol. MI, myocardial infarction.

independent predictor of resuscitation outcome. However, it was not possible to determine what factors were responsible for this change.

Those patients dying before the 48th hour mark appear to have sustained a more severe injury. Although this time point may appear somewhat arbitrary, this choice of cut point is supported by several facts. By about 48 h after injury, plasma volume is restored in successfully resuscitated patients [21]. Patients dying before this point most likely die of hypovolemic shock, whereas those dying after this point most likely die of multiple system organ failure and overwhelming infection.

To our knowledge, this is the first application of ordinal logistic regression to burns outcomes. Other examples from the surgical and critical-care literature include development of models predictive of the following ordinal outcomes:

- Destination of elderly patients admitted to the ICU (discharge to home, discharge to a nursing or rehabilitation facility, or death) [22].
- Injury severity following air-bag deployment [23].
- Severity of illness of septic infants [24].
- Glasgow Outcome Score for patients with subarachnoid hemorrhage [25].

In addition to ordinal logistic regression, there are other approaches to modeling outcomes with multiple ordinal outcomes, which employ binomial logistic regression. One can model several dichotomous outcomes separately. In the present study, for example, it would be possible separately to consider FAIL versus NONFAIL/LIVE, and FAIL versus NONFAIL/DIE patients [26]. Alternatively, one can collapse down, or “dichotomize,” the data into two outcomes: in the present study, for example, consider FAIL versus all patients who lived for more than 48 h (NONFAIL) [27]. Although often useful, these binomial approaches entail the loss of potentially useful data [26,28] and require the careful selection of the optimal cut-point [27].

Validation of an outcome predictor ideally entails prospective application of the predictor to new data; this was not done in this study because of the small number of FAIL patients. The inclusion of year of injury in our predictor suggests, however, that changing patient-care practices over time may introduce error into prospective outcome prediction. Relatedly, the poor performance of the predictor in accurately categorizing the FAIL patients may reflect the small number of patients (62) in that category.

Few reports have examined the problem of do-not-resuscitate (DNR) orders in burn patients. An examination of Table 3 suggests that in many cases the presence of a terminal illness in association with severe thermal and inhalation injury made such a choice, in consultation with the next of kin, an obviously reasonable one. These patients are to be contrasted with patients for whom the DNR order is written after resuscitation is complete. Although we did not examine this question in the present study, it is our

impression that in most of these DNR/LATE patients developed evidence of terminal illness, e.g. progressive multisystem organ failure, only later in their hospital course.

## 5. Conclusion

In summary, the usual variables which influence outcome following thermal injury—age, burn size, and inhalation injury—were used to generate an ordinal logistic regression model predictive of failure of burn resuscitation. The overall accuracy of the model was 91.6%, but this reflected accuracy in categorizing survivors (97.7% accuracy for this subgroup), rather than accuracy in categorizing patients who survived resuscitation but died later (57.5% accuracy), or patients who failed resuscitation (16.1% accuracy). As pointed out by P.G. Shakespeare [29] and others, application of outcome predictors to individual cases is fraught with scientific and ethical difficulty. We may be able to predict a high likelihood of death, but we cannot yet predict with certainty that a particular patient will die until that event is well underway. Further work is needed in order to permit earlier identification of those individual characteristics predictive of a poor outcome following thermal injury, and institution of therapy directed at those characteristics.

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